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Brief Clinical Report

Fanconi Anemia in Brothers Initially Diagnosed With VACTERL Association With Hydrocephalus, and Subsequently With Baller-Gerold Syndrome

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Two brothers with presumed Baller-Gerold syndrome, one of whom was previously diagnosed with the association of vertebral, cardiac, renal, limb anomalies, anal atresia, tracheo-esophageal fistula (VACTERL) association with hydrocephalus, were evaluated for chromosome breakage because of severe thrombo cytopenia in one of them. Spontaneous and clastogen-induced breakage was markedly increased in both patients as compared to control individuals. Clinical manifestations and chromosome breakage, consistent with Fanconi anemia, in patients with a prior diagnosis of either Baller-Gerold syndrome, reported earlier in one other patient [Farrell et al., 1994: Am J Med Genet 50:98–99], or with VACTERL association with hydrocephalus, recently reported in 3 patients [Toriello et al., 1991: Proc Greenwood Genet Center 11:142; Porteus et al., 1992: Am J Med Genet 43:1032–1034], underline the clinical heterogeneity of Fanconi anemia and raise the question of whether these syndromes are distinct disorders or phenotypic variations of the same disease.

KEY WORDS: Fanconi anemia, Baller-Gerold syndrome, VACTERL association with hydrocephalus, chromosomal breakage

INTRODUCTION

Two brothers with multiple congenital anomalies were previously diagnosed with Baller-Gerold syndrome, based on their phenotypic appearance and multiorgan abnormalities. The older patient initially carried the diagnosis of the association of vertebral, cardiac, renal, limb anomalies, anal atresia, tracheoesophageal fistula (VACTERL) association with hydrocephalus. A firstborn sister had died on the first day of life due to a hypoplastic left heart. Six digits were noted on all four limbs, but no specific genetic diagnosis was made. Unexplained thrombocytopenia and megakaryocytopenia in the older brother led to chromosome instability studies documenting markedly elevated spontaneous and clastogen-induced breakage consistent with Fanconi anemia. Subsequent cytogenetic studies on the younger brother supported the genetic diagnosis in this family.

CLINICAL REPORTS

Patient 1

This boy is the second, and first surviving, child born by spontaneous vaginal delivery at 36 weeks of gestation to nonconsanguineous parents. Birth weight was 2,350 g, and length was 46 cm. Hydrocephalus had been noted on fetal ultrasound studies, requiring placement of a ventriculoperitoneal shunt shortly after birth, followed by further surgery for coronal craniosynostosis and removal of an occipital cyst (Fig. 1). Additional anomalies, noted at birth, included a ventricular septal defect which subsequently closed spontaneously, hypoplasia of the right and complete absence of the left thumb (Fig. 2), hypospadias with chordee, a horseshoe kidney, and anal atresia. Routine chromosome analysis showed an apparently normal karyotype, and a complete blood count was normal. Moderate thrombocytopenia was first noted at age 14 months. The patient came to our attention at age 31 months when he presented with small bowel obstruction related to previous surgery, severe failure to thrive, mod-

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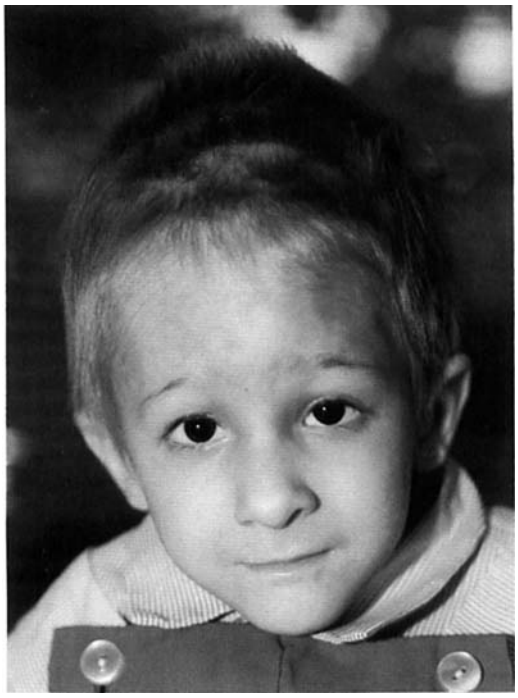

Fig. 1. Patient 1 at age 35 months.

erate anemia, and severe thrombocytopenia. Chromosome instability testing showed increased spontaneous breakage (23-fold increase over control) and 14-fold (Mitomycin C) to 22-fold (Diepoxybutane) increase in hypersensitivity to alkylating agents that induce increased chromosome damage in affected individuals (Table I).

TABLE I. Chromosome Breakage Studies*

Patient	Spontaneous	Mitomycin C	Diepoxybutane
Patient 1	23.0 ×	14.4 ×	22.5 ×
Patient 2	9.0 ×	18.3 ×	25.0 ×

*Breakage frequency compared to normal control.

Patient 2

The younger brother was born at 40 weeks of gestation with a birth weight of 2,590 g and a length of 48 cm (Fig. 3). Complex congenital heart defect with truncus arteriosus, interrupted aortic arch, and ventricular septal defect were diagnosed. Colpocephaly, absence of both thumbs, hypospadias with chordee, and imperforate anus were noted. His presentation was thought to be consistent with Baller-Gerold syndrome. No hematologic abnormalities have become apparent at age 13 months; however, chromosome breakage studies demonstrated a 9-fold spontaneous breakage increase compared to the control, and 18–25-fold increase in clastogen-induced breakage.

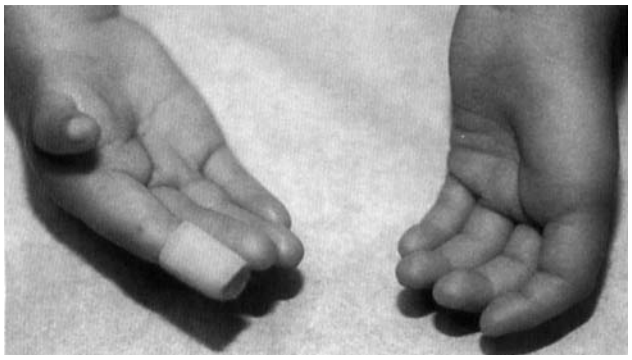

Fig. 2. Hands of patient 1.

DISCUSSION

Fanconi anemia is a congenital syndrome with great variability in phenotypic expression [Glanz and Fraser, 1982]. Affected individuals may appear normal and may not be diagnosed until hematopoiesis is compromised in later life, usually not apparent before age 5–10 years [Butturini et al., 1994]. Alternatively, patients may present with growth and neurocognitive impairment and skeletal malformations, including hypoplasia or aplasia of thumb or radius. Other organ systems may be involved as well. The condition is considered an autosomal-recessive trait. The diagnostic procedure of choice involves evaluation of spontaneous and clastogen-induced chromosome breakage, which is markedly increased compared to normal controls.

Baller-Gerold syndrome is a much rarer disorder, presumably also autosomal-recessive in nature. Only 20 patients have been reported in the world literature. Major manifestations are craniosynostosis and preax-

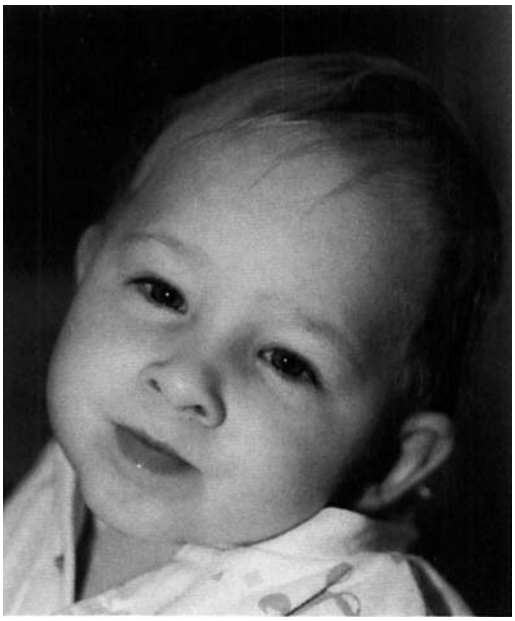

Fig. 3. Patient 2 at age 16 months.

ial upper limb malformations, features also seen in Fanconi anemia [Lin et al., 1993]. It has been pointed out [Galea and Tolmic, 1990] that a subgroup of patients with this disorder have only these two anomalies, while others also present with growth impairment, mental retardation, and congenital heart disease, resembling those anomalies also encountered in Fanconi anemia patients. Abnormalities of hemopoiesis are not known to be part of Baller-Gerold syndrome, and evaluation for possible Fanconi anemia has therefore not necessarily been part of the diagnostic work up, despite the many striking similarities between these disorders.

A genetic condition, to be considered in the differential diagnosis of Baller-Gerold syndrome, is VACTERL association with hydrocephalus. Typical manifestations of this rare disorder include slow development, radial dysplasia, renal anomalies, and ventricular septal defects, all seen also in Baller-Gerold syndrome. Anal atresia, interestingly, is rarely present [Sujansky and Leonard, 1983; Iafolla et al., 1991]. Three patients initially thought to have VACTERL association with hydrocephalus recently had to be rediagnosed with Fanconi anemia [Toriello et al., 1991; Porteus et al., 1992]. Farrell et al. [1994] reported on a 3-year-old girl initially diagnosed in infancy as having Baller-Gerold syndrome associated with congenital hydrocephalus [Lewis et al., 1991]. Recent onset of thrombocytopenia led to chromosomal fragility testing with results consistent with Fanconi anemia. Rediagnosis in this patient, and in the 2 brothers reported here, raises the question of whether these disorders are separate entities or variable phenotypic expressions of the same genetic syndrome. Among the other 19 previously reported patients with Baller-Gerold syndrome, only the initial 2 [Baller, 1950; Gerold, 1959] were older than age 10 years. Four are known to have died in infancy of nonhematologic abnormalities. Longer follow-up may ultimately lead to discovery of hematocytopenias. Rediagnosis of Fanconi anemia in all of these patients further underlines the phenotypic heterogeneity of this syndrome. It appears appropriate to include evaluation of chromosome fragility testing in the diagnostic work-up of both Baller-Gerold syndrome and VACTERL association with hydrocephalus.

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